REMARKS

Claims 9-15 and 17-25 are pending. Claim 9 was amended to recite that the pharmaceutically acceptable additives are selected from the recited list. This amendment is supported throughout the specification and particularly at page 7, line 23-28 of the parent PCT publication, WO 04/043452. Claims 17-24 were withdrawn by the Examiner. However, as explained below, Applicants request rejoinder of these dependent method claims upon allowance of the product claims.

Amendments to the Specification

Applicants are grateful for entry of the amendments to the specification submitted February 27, 2007. No new matter was added in these amendments. A clean copy of said amendments, along with a separate sheet stating that no new matter has been added by this amendment accompanies the instant response.

Restriction Requirement

The Examiner has required restriction of the claims under 35 U.S.C. § 121. More specifically, the Examiner has required restriction to one of the following groups, as described below:

Group I	Claims 9-13, drawn to a pharmaceutical composition for oral administration.
Group II	Claims 14-15 and 25, drawn to a kit.
Group III	Claims 17-24, drawn to a method of treating a subject with a pathology due to organic deficiency of triiodothyronine.

Applicants hereby elect the claims of Group I (claims 9-13) with traverse. Applicants submit that the claims of Groups I and II can be searched together by the Examiner without undue burden.

Indeed, claims 14 and 15 of Group II were searched along with claims 9-13 of Group I in the 11/29/06 office action and in the instant office action claims 14, 15 and 25 were not withdrawn by the examiner. Thus, Applicants respectfully request withdrawal of the restriction requirement regarding Groups I and II. Furthermore, Applicants believe that the claims of Groups I and III can also be searched together without undue burden because a search for the claimed compounds themselves would necessarily uncover art relating to the methods of use. Thus, Applicants request withdrawal of the restriction requirement in its entirety.

In the even that the restriction requirement is maintained in whole or in part, Applicants request rejoinder of the dependent kit and/or method claims once the product claims are allowed.

Rejections Under 35 USC§112, ¶ 2

Applicants are grateful for the withdrawal of the rejection of claims 3, 5, 15 and 16. The rejection of claims 9 and 10-13 for alleged indefiniteness was maintained due to recitation of the phrase "such as". While Applicants submit that as drafted the claim is sufficiently definite, solely to expedite prosecution, Applicants have amended claim 9 to delete this language and believe that the claims amendments render this rejection moot.

Rejections Under 35 USC§ 103

Applicants thank the Examiner for the withdrawal of the rejection of claims 1-7, 9 and 16 for alleged anticipation, and the withdrawal of the rejection of claims 8 and 10-15 for alleged obviousness.

Claims 9-15 and 25 stand rejected under 35 U.S.C. 103(a) for alleged obviousness over Lopresti et al, J. of Clinical Endocrinology and Metabolism, Vol 73, No. 4, 1992, pages 703-709 ("Lopresti") in view of Mol et al ("Mol") and Herfindal et al, In:Clinical Pharmacy and Therapeutics, 1992, pages 289-291 ("Herfindal"), and further in view of Fisher et al US 4,254,095 ("Fisher").

The Examiner asserts that Lopresti discloses oral administration of T3S and that in view of Fisher the dose disclosed in Lopresti overlaps with the instant claims. Thus, the Examiner concludes that "[i]n view of the teaching of Lopresti et al., the dosage amounts of T3S recited in claims 9, 10, 11, 12, 13 15 and 25 are reasonably construed to be dose optimization and within the skill and scope of knowledge[of] an artisan skilled in the art." P. 9-10 Similarly, the examiner concludes that the subject matter of claim 14 is also allegedly within the skill in the art in view of

Lopresti. Finally, the examiner concludes that the kits of claims 14, 15 and 25 are allegedly obvious over Lopresti n view of Hefindal and Mol.

Applicants respectfully disagree. As an initial matter, Lopresti does **not** disclose oral administration of T3S. Rather, Lopresti confirms the expectation of the skilled artisan that T3S would not be absorbed by the GI tract given that it bears the highly polarized/ionic group – OSO_3H. Specifically, in order to determine whether T3S is absorbed after oral administration, Lopresti administered a 1% aqueous human albumin solution of labelled T3S (see page 704, 2nd column, 3rd paragraph to the bottom) to two subjects.[1] Importantly, as a result of this study Lopresti concluded "No labelled T3S was detected in the serum of patients after oral ingestion of labelled T3S" (see page 707, 1st column); and, also: "no absorption of intact (labelled) T3S was detected after its oral ingestion" (see half of 2nd column of the abstract). Thus, Lopresti teaches away from the claimed invention. One skilled in the art aware of the possible thyromimetic activity exerted by T3S and of Lopresti could not have expected T3S to be properly absorbed upon oral ingestion so as to get an oral thyromimetic drug and thus would not have been induced by Lopresti to provide the novel oral compositions of the invention.

Because of the above, and contrary to the Examiner's statement (see bottom of page 9), the dosage amounts of oral T3S of the instant claims cannot be regarded as being derivable (e.g. dose optimization) from Lopresti, which comes to a completely different result: no absorpion of T3S upon its oral administration.

Furthermore, Applicants note that 1μCi does **not** correspond to 1 microgram. A μCi is a measurement of radioactivity. A μg is a measurement of weight. Claim 18 of Fisher provides the specific activity of a [^{125}I] labelled substance, conventionally expressed in terms of micro curie/microgram, that is to say micro curie per microgram (μCi per μg). Fisher teaches that 1 microgram of a labelled substance emits a given amount of radiation expressed in micro curies (μCi); however, this does not mean that 1 μCi corresponds to 1 microgram. Thus, contrary to the Examiner's opinion, the teaching of Lopresti in combination with Fisher does not suggest an oral composition of T3S at a dose ranging from 5 to 1000 μg, as in the instant claims.

The secondary references cited by the Examiner do not cure these deficiencies. Neither Herfindal nor Mol discloses or suggests oral administration of T3S.

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[1] Labelled T3S differs from T3S because of the presence of radioactive iodine atoms, [^{125}I], a well-known iodine isotope used for labelling purposes.

Herfindal et al. teaches thyroid preparations among which are T3 and T4 preparations in the treatment of patients with hypothyroidism. This information and the well known drawbacks to use of T3 and T4 as thyromimetic drugs is discussed in the instant specification. (see page 5; page 6, lines 13-15 and 22-24).

Mol et al. teaches sulfate esters of iodothyronine and their preparation and that, as the Examiner pointed out, the availability of large amounts of these compounds may facilitate the study of the importance of sulfate conjugation in the metabolism of thyroid hormones.

However, neither of theses references teaches or suggest that T3S compositions could be administered orally and provide thyromimetic activity. Furthermore, as Lopresti, who actually investigated the thyromimetic activity and metabolism of T3S, showed it would not be absorbed upon oral administration, the claimed compositions must be regarded as unpredictable and unexpected over the aforementioned prior art references, either taken alone or in combination.

The Claimed Compounds are Unexpectedly Advantageous Compared to the Prior Art

As shown in the Experimental Data and Figures 1-5, attached as Exhibit 1, Applicants established that, contrary to the expectation of the art, T3S may be administered and absorbed by the oral route. In addition, because of the optimal absorption profile from the G.I. tract, the claimed orally administered compositions and kits advantageously enable maintenance of steady levels of T3 in the body for prolonged periods of time (e.g. for up to 24 hours). This is particularly advantageous in therapy where the goal is to supplement thyroid hormone in its most active form, T3, at a steady level.

Indeed, as shown in Figures 1 and 2, upon oral administration of T3S, its plasma concentration markedly increased, thus showing an unexpectedly optimal absorption profile from the G.I. tract. Plasma concentrations, in particular, were detectable shortly after the administration of T3S and the highest amounts, in plasma, were reached 4-8 hours after administration. Then, plasma concentrations of T3S slowly decreased, but were detectable 24 hours after administration. In contrast plasma concentrations of T3S administered peritoneally peaked from 2 to 4 hours after injection (see Figure 4).

To show that plasma concentrations are dose dependent see, as per Figure 3, the results obtained at particularly high doses of oral T3S (70 μg/kg). As before, optimal absorption of T3S

from the G.I tract was observed and highest plasma levels were detected 4-8 hours after administration.

In support of the thyromimetic activity exerted by oral T3S, plasma concentrations of T3 were also detected after oral administration (21 μg/kg) to thyroidectomised rats (see Figure 5). Interestingly, an almost constant transformation of T3S into T3 was observed after oral administration.

CONCLUSION

In view of the preceding remarks, it is believed that claims 9-15 and 25 are in condition for allowance. Applicants request rejoinder of claims 17-24.

If there are any questions remaining as to patentability of the pending claims, Applicants would very much desire to have a telephonic interview. The Examiner is invited to contact Applicants' undersigned attorney at the number below.

No fee is believed to be due with the filing of this Amendment. However, if any fees are deemed necessary, the Director is hereby authorized to charge such fees to Deposit Account No. 50-2168.

Favorable action is respectfully requested.

Respectfully submitted,

Dated: January 30, 2008

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EXHIBIT 1

Experimental Data

To investigate the pharmacokinetic profile, T3S was administered, as a single dose, to rats eiether orally or intraperitoneally.

1. Oral Administration

T3S was orally administered as a single dose of either 7 μg/kg (Figure 1) or 21 μg/kg (Figure 2) to to thyroidectomised sprague Dawley rats. Plasma concentrations of T3S were monitored. Plasma concentrations of T3S were detectable shortly after the administration of T3S and the highest amounts, in plasma, were reached 4-8 hours after administration. Then, plasma concentrations of T3S slowly decreased, but were still detected 24 hours after administration. In sum, as shown by Figures 1 and 2, TS3 plasma concentration markedly increased after oral administration, showing an optimal absorption profile from the G.I. tract.

T3S was also administered orally as a single dose of 70 μg/kg. As in Figures 1 and 2, optimal absorption of T3S from the G.I. tract was observed and the highest plasma levels were detected 4-8 hours after administration. See Figure 3. Comparison of Figures 1-3 shows that plasma concentrations are dose dependent.

2. Intrapaeritoneal Administration

T3S was administered intraperitoneally as a single dose of 7 μg/kg to thyroidectomised sprague Dawley rats. Plasma concentrations of T3S were monitored. Plasma concentrations of T3S were detectable shortly after the administration of T3S, peaked from 2 to 4 hours after injection and quickly decreased. (Figure 4)

3. Thyromimemtic Activity of Orally Administered T3S

T3S was orally administered orally as a single dose of 21 μg/kg to to thyroidectomised sprague Dawley rats. Plasma concentrations of T3S and T3 were monitored. Plasma concentrations of T3 were detected after roral administration (see Figure 5) and an almost constant transformation of T3S into T3 was observed.

Discussion

The above data clearly establish that T3S may be unexpectedly administered by the oral route. In addition, because of the optimal absorption profile from the G.I. tract, the oral administration advantageously enables maintenance of essentially steady levels of T3 in the body, for a prolonged period of time (e.g. up to 24 hours). This latter finding is particularly advantageous in therapy, in those cases in which it is needed to supplement thyroid hormone in its most active form, e.g. as T3, which as explained in the instant application, cannot be achieved by administration of T3 itself (see the application as filed, bottom of page 5; page 6, lines 13-15 and 22-24).

Figura 1. Plasma concentrations after oral administsration of T3S 7 μg/kg (mean ±SD)

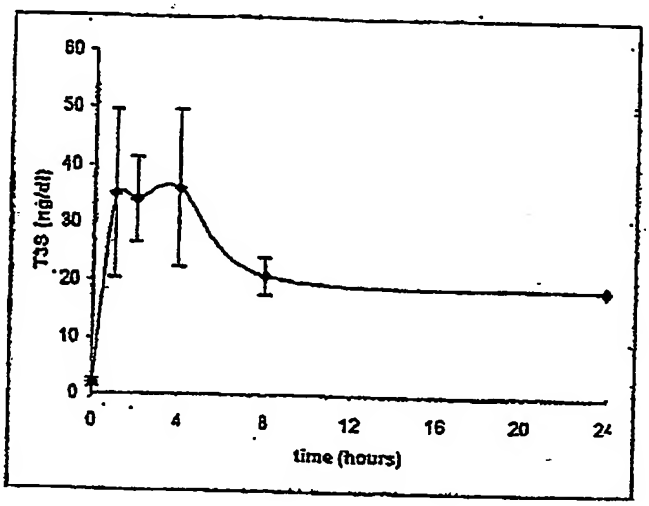

Figura 2. Plasma T3S concentrations after oral administration of T3S 21μg/kg (mean±SD)

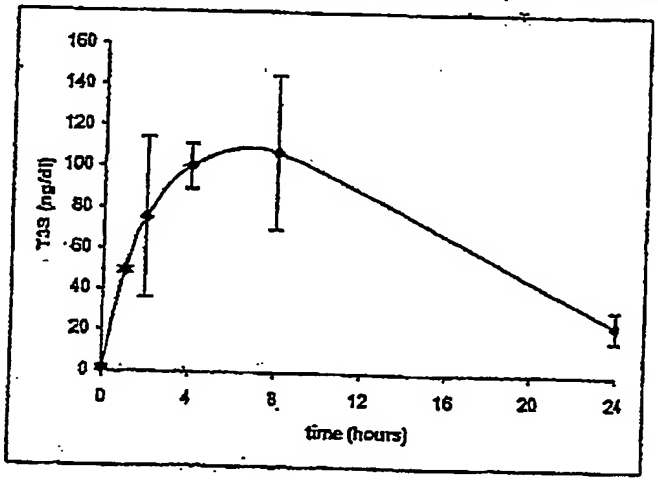

Figura 3. Plasma T3S concentrations after oral administration of T3S 70μ g/kg (mean ±SD)

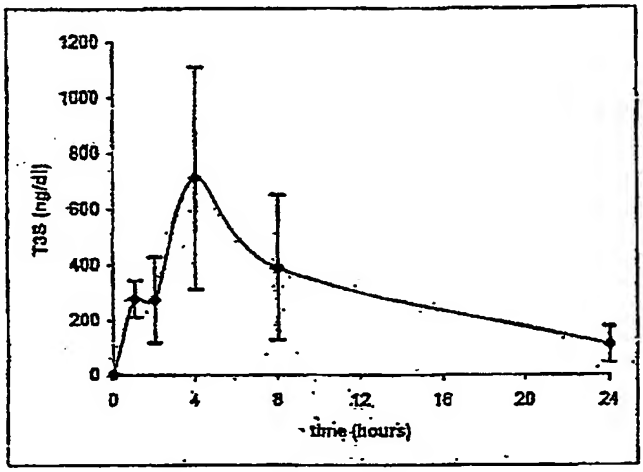

Figura 4. Plasma T3S concentrations after intraperitoneal administration of T3S 7μ g/kg (mean ±SD)

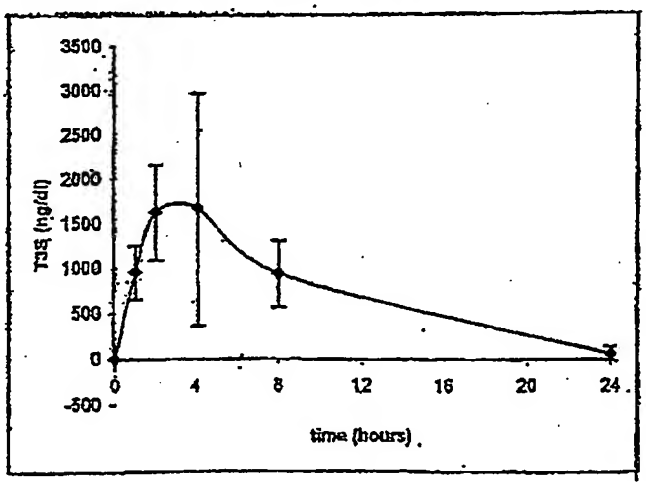

Figura 5. Plasma concentrations of T3S and T3 after oral administration of T3S 21 µg/kg (mean ±SD)